non-elected species previously withdrawn from consideration must be rejoined and examined for patentability (MPEP 809).

Regarding the rejection of claims 1 to 26 under 35 U.S.C. § 102(a) over Klein et al.

The rejection of claims 1 to 26 under 35 U.S.C. § 102(a) over Klein et al. is respectfully traversed. The Office Action alleges that Klein et al. report contacting RAR-RXR heterodimers with the agents 193109 and 193840, and measurement of coactivator and corepressor association as shown in Figures 4A and 4B. The Office Action concludes that Klein et al. anticipate the invention.

Klein et al. cannot anticipate the invention since they fail to teach that an effective agent that dissociates nuclear hormone receptor activities can be identified by the combination of coactivator association combined with corepressor association as claimed. Neither do Klein et al. teach any such effective agents that achieve both coactivator association and corepressor association to a given test complex. Klein et al. merely compare the ability of AGN193109 and AGN193840 to recruit corepressor, or coactivator, to RARβ complexes. Yet neither of the agents described in Klein et al. achieve coactivator association combined with corepressor association, as required to identify an effective agent of the invention. Specifically, AGN193109 treatment of RARβ complexes appears to result in N-CoR corepressor recruitment but not SRC-1 recruitment to the complexes. See, for example, Klein et al. at Figure 5A, right

panel, and page 19406, second column, first incomplete paragraph, which indicate that AGN193109 did not recruit SRC-1 to the RARβ complex. Similarly, treatment of RARβ complexes with the second agent, AGN193840, appears to result in minimal SRC-1 coactivator recruitment but not an increase in N-CoR corepressor recruitment. See, for example, page 19405, Figure 4C, right panel, and Figure 4D, lane 5, which indicate that N-CoR recruitment to RARβ was not detectable ("ND"). Thus, neither of the agents described in Klein et al. result in coactivator association combined with corepressor association, as recited in the claimed methods.

In sum, not only do Klein et al. fail to teach that an effective agent which dissociates nuclear hormone receptor activities can be identified by the combination of coactivator and corepressor association with a given test complex, the cited publication fails to describe any such effective agents. Absent such teachings, the cited reference by Klein et al. cannot anticipate the invention. In view of the above remarks, Applicants respectfully request that the Examiner remove the rejection of claims 1 to 26 under 35 U.S.C. § 102(a) over Klein et al.

Regarding the rejection of claims 1 to 26 under 35 U.S.C. § 102(b) over DiRenzo et al.

The rejection of claims 1 to 26 under 35 U.S.C. § 102(b) over DiRenzo et al. is respectfully traversed. The Office Action indicates that DiRenzo et al. determine the effect of TTNPB on recruitment of coactivator and corepressor to the

PPAR and RAR receptors (Figure 6, page 2173), alleging that DiRenzo et al. therefore anticipate the invention.

Applicants submit that claims 1 to 26 are novel over DiRenzo et al.'s description of PPARγ receptor assays. In particular, Figure 6 of DiRenzo et al. appears to describe analysis of N-CoR association with the PPARγ receptor but fails to describe analysis of SRC-1 association to this receptor. Given that the claims require assaying a test complex containing nuclear hormone receptor dimer for both coactivator and corepressor association, the PPARγ assays of DiRenzo et al. cannot anticipate the invention.

The RARα assays of DiRenzo et al. also cannot anticipate the invention. In particular, the methods of the invention are practiced by contacting a nuclear hormone receptor with one or more agents "under conditions suitable for forming a test complex comprising nuclear hormone receptor dimer" (step (a) of each independent claim; emphasis added). In the case of RARα, which is well known to act as a heterodimer with RXR, such suitable conditions would include a source of RXR. See, for example, page 2166, abstract, of DiRenzo et al., which reports that RXR forms heterodimers with RAR and PPAR and that RXR is an obligate member of most nuclear receptor heterodimers. In contrast to the invention, which requires conditions suitable for forming a test complex containing nuclear hormone receptor dimers, DiRenzo et al. fail to provide a source of RXR to the RARα/SRC-1 recruitment assay of Figure 6B. DiRenzo et al. instead describe an assay for SRC-1 recruitment performed using

baculovirus-expressed N-CoR, bacterially expressed RARα and *in vitro* translated SRC-1 in the absence of a source of RXR (see legend to Figure 6). In the absence of "conditions suitable for forming a test complex comprising nuclear hormone receptor dimer," the RAR assays of DiRenzo et al. cannot anticipate the invention.

Further in regard to the RAR assays of DiRenzo et al., the cited reference fails to identify an "effective agent that dissociates nuclear hormone receptor activities" as in the claimed methods. As disclosed in the subject application, such an effective agent has selective activity on an indirect signaling pathway while lacking or having significantly reduced transcriptional activity at genes regulated through cognate response elements (see specification at page 13, lines 24-31). At best, DiRenzo et al. describe the agent TTNPB, which is a potent transactivator at RAR cognate response elements and, thus, is not an "effective agent that dissociates nuclear hormone receptor activities." That TTNPB transactivates through cognate response elements is supported in the specification, for example, at page 51, lines 22-23, which indicates that TTNPB is an RAR agonist, and in Figure 3A, which shows potent transactivation of an estrogen receptor (ER) DNA binding domain/RARα ligand-binding domain chimera through ER response elements (see Figure 3A; page 62, lines 12-17; and page 64, line 25, to page 65, line 6). Given the demonstrated ability of TTNPB to transactivate through nuclear hormone receptor cognate response elements, TTNPB is not an effective agent that dissociates nuclear hormone receptor

activities as recited in claims 1 to 26. Accordingly, DiRenzo et al. further cannot anticipate the invention.

In view of the above remarks, Applicants respectfully request that the Examiner remove the rejection of claims 1 to 26 under 35 U.S.C. § 102(b) over DiRenzo et al.

Regarding the rejection of claims 1 to 26 under 35 U.S.C. § 103 over DiRenzo et al.

The rejection of claims 1 to 26 under 35 U.S.C. § 103 over DiRenzo et al. is respectfully traversed. DiRenzo et al. allegedly describe determining the effect of TTNPB on recruitment of SRC-1 coactivator and N-CoR corepressor to the RAR and PPAR receptors. The Office Action asserts that practicing the methods of the invention with TIF-2 coactivator would have been obvious based on the suggestion that other members of the SRC-1 family of coactivators such as TIF-2 also may serve as coactivators for nuclear hormone receptors.

In contrast to the claimed invention, DiRenzo et al. do not teach or suggest an effective agent that dissociates nuclear hormone receptor activities or identification of such an effective agent by coactivator association combined with corepressor association. At best, DiRenzo et al. describe analysis of RARα and the agent TTNPB, which, as described above, is not an effective agent that dissociates nuclear hormone receptor activities due to its demonstrated ability to transactivate through cognate response elements. Absent a

teaching or suggestion of an effective agent that dissociates nuclear hormone receptor activities and further absent identification of an effective agent by coactivator association combined with corepressor association, the claimed methods are unobvious over the cited reference. In view of the above, Applicants respectfully request that the Examiner remove the rejection of claims 1 to 26 under 35 U.S.C. § 103 over DiRenzo et al.

CONCLUSION

In light of the remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, he is invited to call the undersigned agent or Cathryn Campbell.

Respectfully submitted,

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